that in the future a therapeutic approach to chronic liver disease would consist of a number of complementary approaches considering the multitude of pathogenic mechanisms.[3] Silybin is a natural flavonoid that has been conjugated to vitamin E and phospholipids to improve its bioavailability, and antioxidant and antifibrotic activity.[4]

After approval of the ethics committee and informed consent, 85 outpatients were consecutively enrolled in the study: 59 were affected by primitive NAFLD (group A) and 26 by HCV related chronic hepatitis C in combination with NAFLD, all HCV genotype 1b, and non-responders to previous antiviral treatment (group B). All patients with a diagnosis of liver disease in the two years prior to the study, according to histological criteria,[5 6] were enrolled over six consecutive months and further divided into two subgroups using a systematic random sampling procedure: 53 (39 NAFLD and 14 HCV) were treated with 4 pieces/day of the complex silybin-vitamin E-phospholipids (Realsil (RA); IBI-Lorenzini Pharmaceutical, Italy) for six months followed by another six months of follow up, while the other 32 patients (20 NAFLD and 12 HCV) served as a control group (no treatment). One piece contained 94 mg of silybin, 194 mg of phosphatidylcholine, and 90 mg of vitamin E.

At 0, 6, and 12 months, we evaluated: body mass index (BMI), bright liver by ultrasonography (US), aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl-transpeptidase (γGT) levels, blood glucose and insulin plasma levels with a contemporaneous determination of insulin resistance by HOMA test[7] and, as indices of liver fibrosis, plasma levels of transforming growth factor β, hyaluronic acid, and metalloproteinase 2, by commercial ELISA kits.[8] Results were analysed by ANOVA, the Wilcoxon and χ^2 tests to evaluate differences among groups and percentages of frequency, and by the Pearson bivariate correlation test to evaluate correlations among data.

There were no adverse events during the treatment and study compliance was absolute. All patients were asked to follow a well balanced individual diet during the study. BMI increased in approximately 70% of cases under basal conditions and did not vary significantly between groups, with the exception of HCV treated patients. In fact, only in this group, at six and 12 months, did the percentage of overweight patients decrease significantly (44%; p<0.01 v basal and other group data). US steatosis, graded from 0 to 3,[9] was significantly improved in the NAFLD treated group (p<0.01 v others). Table 1 summarises the other results.

Liver enzyme levels showed an improvement in treated individuals but this only persisted in group A. Hyperinsulinaemia, present in both groups, was significantly reduced only in treated patients. Treatment with RA significantly reduced all indices of liver fibrosis in both treated groups, with a persistent effect only in group B.

A significant correlation among indices of fibrosis, BMI, insulinaemia, degree of US steatosis, and γGT was found (p<0.01). Despite two main drawbacks in this study (absence of a placebo treatment and no histological examination at the end of the study), the data suggest that this new complex of silybin-vitamin E-phospholipids should be tested in a well controlled larger trial to further confirm its possible therapeutic effect on insulin resistance and liver damage, particularly when other drugs are not indicated or have failed, or as a complementary treatment associated with other therapeutic programmes.

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Is the periodic repetition of a coagulation check necessary during anti-hepatitis C virus therapy?

Peginterferon α and ribavirin have become the mainstay of treatment for chronic hepatitis C virus (HCV) infection.[1] However, chronic use of interferon (IFN)-α has been associated with the development of autoimmune disorders, such as systemic lupus erythematosus, autoimmune haemolytic anaemia, and autoimmune thyroiditis. In particular, some reports have documented the development of acquired factor VIII inhibitors in patients receiving IFN-α, including those treated for chronic HCV infection.[2–6]

We report the case of a 49 year old male patient treated for chronic active HCV related cirrhosis. He received a six month course of peginterferon α2a at a dose of 180 μg weekly and ribavirin at a dose of 800 mg daily for three months only, due to a marked decrease in haemoglobin level, obtaining a complete viral response. Before therapy, activated partial thromboplastin time (aPTT) and prothrombin time-international normalised ratio (PT-INR) values were in the normal range (aPTT ratio 1.28 and INR 1.11). Due to abnormal bleeding during a routine dental treatment performed at the end of antiviral treatment in September 2005, the patient underwent a coagulation screening which revealed a prolonged aPTT (2.14; normal range 0.85–1.17). Coagulant factor VIII level was reduced (FVIII:C 17%; normal range 50–150%) and a mixing study demonstrated the presence of a low titre inhibitor (1.6 Bethesda units/ml). Response to subcutaneous injection of desmopressin at a dose of 0.3 mg/kg was satisfactory as FVIII:C increased to 70% and aPTT normalised four hours after injection. Recent tests performed three months after the end of antiviral treatment (November 2005) were unchanged.

If our case report provides further evidence in favour of the association between chronic exposure to peginterferon and the development of acquired factor VIII inhibitors, it raises several important questions too. Firstly, what is the real incidence of this phenomenon in patients treated for HCV infection? Are these inhibitors so rare as initially believed or are they misdiagnosed? Are they clinically relevant, what is the natural history of the coagulative alteration (that is, do they require treatment or do they tend to disappear spontaneously), and which is the best treatment? In our opinion, a response to these concerns may be obtained only through a careful coagulation study (especially aPTT ratio) of these patients during and after IFN treatment.

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